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Investigating clinical and laboratory findings and mortality rates among vaccinated and unvaccinated COVID-19 inpatients

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ABSTRACT

Aim: COVID-19 is an important public health problem in world and Turkey. The present study aimed to compare the clinical and laboratory findings and mortality rates among vaccinated and unvaccinated COVID-19 inpatients.

Material and Method: We included patients receiving inpatient treatment in COVID-19 wards of our hospital between April 25 and October 22, 2021. The patients were divided into two groups: those with and without the COVID-19 vaccine. We extracted patient information from anamnesis files and the hospital information system. Then, we recorded the patients' epidemiological and laboratory findings and vaccination status. Patients with at least two doses of the COVID-19 vaccine were considered "vaccinated." We performed Fisher's exact test and Chi-square test to analyze the data. All statistical analyses were performed in SPSS, and a p-value <0.05 was accepted as statistically significant.

Results: The study included 63 vaccinated and 83 unvaccinated patients. With a mean age of 71.4±12.3 years, thirty (47.6%) of the vaccinated patients were females, and 33 (52.3%) were males. Of the unvaccinated ones, 40 (48.1%) were females, while 43 (51.8%) were males (mean age=52.2±14.4 years). The mean age was significantly higher in the vaccinated group than in the unvaccinated group (p<0.01). While 82.5% of the vaccinated patients received two doses, 17.5% received three doses of the COVID vaccine. Besides, 95.3% of the patients received their first dose of inactivated vaccine (Sinovac, China) and 4.7% of an mRNA vaccine (BioNTech, Germany). We found that comorbidities were significantly more prevalent in the vaccinated group than in the unvaccinated group (44 (69.8%) vaccinated and 34 (40.9%) unvaccinated patients had a comorbid disease, p<0.01). Among the accompanying diseases, hypertension was significantly more prevalent in the vaccinated group than in the unvaccinated group (p<0.01). Considering their laboratory findings, the vaccinated patients had significantly higher leukocyte, troponin, and ferritin values than the unvaccinated patients (p=0.008). Consequently, five (57.9) of the vaccinated patients and 4 (4.8%) of the unvaccinated patients died (p=0.05).

Conclusion: Similar mortality rates between our vaccinated and unvaccinated patients may be attributed to the fact that the vaccinated group was relatively older, had more comorbid diseases, and received their second dose after an average of 100.6 days following their first dose of inactivated vaccine. In conclusion, further clinical research involving more cases that received different COVID-19 vaccines is needed to uncover the factors affecting mortality and morbidity among vaccinated patients.

Keywords: COVID-19, vaccine, mortality, morbidity

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INTRODUCTION

The causative agent of the novel Coronavirus disease-2019 (COVID-19) is SARS-CoV-2, an enveloped RNA virus leading to a pandemic worldwide. As of July 1, the World Health Organization (WHO) reported the total number of confirmed COVID-19 cases as 545,226,550, the number of COVID-19 deaths as 6,334,728, and the number of doses administered all over the world as 11,986,040,938. As of the same date, Turkey reported the total number of COVID-19 cases to be 15,123,331, the total number of deaths to be 99,032, the number of new cases in the last one week to be 26,635, and the number of deaths in the last one week to be 17. Accordingly, Turkey ranked 10th in the number of total cases and mortality rates (1). COVID-19 disease may follow diverse clinical courses from asymptomatic infection to mild upper respiratory tract infection and from mild to severe viral pneumonia that may result in death (2, 3). Major risk factors for severe COVID-19 disease are age, male sex, obesity, smoking, and comorbid chronic conditions such as hypertension (HT) and diabetes mellitus (DM). A

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substantial body of research revealed that advanced age appears as the most significant risk factor for the severe COVID-19 disease (2,3-5).

The most efficient methods to control the pandemic are shown as non-drug infection control measures such as vaccination, mask wearing, phyisical distance, and hand washing. A plethora of studies documented that COVID-19 vaccines protect against diseases with a severe course and significantly reduce hospitalization rates in intensive care units (6).

Apart from approved and frequently used vaccines against COVID-19, there are also ongoing scientific trials to develop new vaccines. The available vaccines in clinical use are mRNA vaccines (e.g., BNT162b2 vaccine, Pfizer–BioNTech), recombinant adenovirus vector vaccines (e.g., ChAdOx1-S vaccine, AstraZeneca–Oxford University), and inactivated vaccines (e.g., CoronaVac vaccine, Sinovac Biotech). BNT162b2 and CoronaVac are widely used in Turkey to protect against COVID-19.

The present study aimed to compare the clinical and laboratory findings, mortality rates, and mortality-affecting risk factors between the vaccinated and unvaccinated patients receiving inpatient treatment in the COVID-19 wards of Ankara Training and Research Hospital.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara Training and Research Hospital Clinical Researches Ethics Committee (Date: 10.20.2021, Decision No: E-765/2021). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

We included patients receiving inpatient treatment in COVID-19 wards of Ankara Training and Research Hospital between April 25 and October 22, 2021. The patients were divided into two groups: those with and without the COVID-19 vaccine. Then, we recorded the patients' epidemiological and laboratory findings and vaccination status. While we extracted patient information from anamnesis files, their epidemiological, clinical (tachypnea, oxygen saturation), laboratory (lymphocyte, C-reactive protein, troponin, D-dimer, ferritin), and radiological data were obtained from the hospital information management system. Patients with at least two doses of the COVID-19 vaccine were considered "vaccinated."

We performed Fisher's Exact test and Chi-square test to analyze the data. All statistical analyses were performed in SPSS a p-value < 0.05 was accepted as statistically significant.

RESULTS

The study included 63 vaccinated and 83 unvaccinated patients. With a mean age of 71.4 ±12.3 years, thirty (47.6%) of the vaccinated patients were females, and 33 (52.3%) were males. Of the unvaccinated ones, 40 (48.1%) were females, while 43 (51.8%) were males (Mage=52.2 ±14.4 years). The mean age was significantly higher in the vaccinated group than in the unvaccinated group ($p< 0.01$). While 82.5% of the vaccinated patients received two doses, 17.5% received three doses of the COVID vaccine. Besides, 95.3% of the patients received their first dose of inactivated vaccine (Sinovac, China) and 4.7% of an mRNA vaccine (BioNTech, Germany). We found that comorbidities were significantly more prevalent in the vaccinated group than in the unvaccinated group (44 (69.8%) vaccinated and 34 (40.9%) unvaccinated patients had a comorbid disease, $p< 0.01$). Among the accompanying diseases, HT was significantly more prevalent in the vaccinated group than in the unvaccinated group ($p< 0.01$). Considering their laboratory findings, the vaccinated patients had significantly higher leukocyte, troponin, and ferritin values than the unvaccinated patients ($p=0.008$). Consequently, five (5.79%) of the

Table. Demographic and laboratory findings of the vaccinated and unvaccinated patients having died due to COVID-19

Patient no.	Sex	Age (years)	Concomitant disease	Type of vaccine/number of doses administered/ time since the last dose	Leukocytes (ref.: 4000-10000/mm³)	Lymphocyte count (ref.: 800-4000 mm³)	Troponin (ref.: 0-14ng/mL)	Ferritin (ref.: 13-150 micg/mL)
Dead unvaccinated patients								
1	Female	80	HT,DM, COPD	None	6,640	1,200	25.6	377
2	Female	75	HT, Asthma	None	6,120	370	20.93	173
3	Female	75	COPD	None	9,070	520	41.69	328
4	Female	49	None	None	3,340	610	6.72	608
Dead vaccinated patients								
1	Male	77	HT	CoronaVac/2/104days	10,930	410	29.74	989
2	Female	73	HT	CoronaVac/2/64days	5,500	910	32.6	89.3
3	Male	67	HT,DM	CoronaVac/2/67days	11,170	2,090	39.78	134
4	Female	84	HT, DM, COPD	CoronaVac/ 2/131 days	7,650	2,140	3	82.6
5	Female	70	HT, DM	CoronaVac/ 2/137 days	6,530	900	9.25	507

vaccinated patients and 4 (4.8%) of the unvaccinated patients died (p=0.05). Logistic regression analysis, which was run to reveal risk factors of mortality among the patients, yielded no significant finding, which may be due to the low number of patients having died in the groups. Table shows the demographic and laboratory findings of the vaccinated and unvaccinated patients having died due to COVID-19.

DISCUSSION

The causative agent of the novel type of coronavirus, also known as coronavirus infectious disease 2019 (COVID-19), is SARS-CoV-2, one of the coronaviruses that appeared in Wuhan, China first, and then caused a worldwide pandemic. COVID-19 is a contagious infectious disease caused by SARS-CoV-2, characterized by atypical pneumonia. Most patients with COVID-19 have a mild or moderate course, but 5-10% may experience severe or even a life-threatening course. Disease-related mortality rates are reported as about 2% (7).

Apart from currently available COVID-19 vaccines deployed in the effective fight against the COVID-19 pandemic, scientific trials to develop new vaccines are still ongoing. Vaccines have a vital role in the control of the COVID-19 pandemic. There has been a significant decrease in mortality and morbidity rates thanks to the introduction of COVID-19 vaccines. Yet, underdeveloped countries have experienced problems in the supply of vaccines. In Turkey, the rate of persons fully vaccinated with the last dose of primary series per 100 population has been 63.84 (1). Despite no major difficulties accessing the COVID-19 vaccine, vaccination rates have remained under the desired level worldwide and in Turkey (1, 8).

The relevant research showed that unvaccinated persons have a 13.9 times higher risk of infection and 53.2 times higher risk of COVID-19-related death compared to fully vaccinated persons having received a single booster dose while 4.0 times higher risk of infection and 12.7 times higher risk of death compared to fully vaccinated persons not having received a booster dose (9).

In a cohort study with 19,625 nursing home residents in the United States, individuals vaccinated with the mRNA vaccine (Moderna or Pfizer-BioNTech) were reported to have a lower all-cause mortality rate than unvaccinated individuals. The same study also documented that the risk of mortality did not increase among those receiving the COVID-19 vaccine (10).

In vitro studies on the efficacy and neutralizing antibody levels of COVID-19 vaccines indicated that mRNA and Novavax protein subunit vaccines lead to higher antibody responses than viral vector and inactivated vaccines. Although efficacy rates between 60% and 94% were reported for vaccines used against COVID-19, it was noted that these rates are susceptible to research design, the population studied, and the prevalence of SARS-CoV-2 variants during the study; therefore, a one-to-one comparison between vaccines is not always convenient (6).

A UK-based study demonstrated that vaccination with a dose of BNT162b2 or ChAdOx1-S resulted in a significant reduction in symptomatic COVID-19 and greater protection against severe diseases in older adults. Both vaccines showed similar efficacy, providing protection during follow-up (>6 weeks). Furthermore, the second dose of BNT162b2 was found to be associated with greater protection against symptomatic disease. In addition, both vaccines were reported to have significant efficacy against the B.1.1.7 variant (11).

A national mRNA BNT162b2 (Pfizer-BioNTech) vaccine surveillance study in Israel reported that the COVID-19-related mortality rate decreased by 96.7% in vaccinated individuals. In that study, two doses of the BNT162b2 vaccine were reported to be quite effective in preventing infections (including symptomatic and asymptomatic SARS-CoV-2 and B.1.1.7 SARS-CoV-2 variants), COVID-19-related hospitalizations, severe diseases, and death in all age groups, including adults over 16 years and older adults over 85 years) (12).

Another study reported that receiving the mRNA COVID-19 vaccine significantly reduces the possibility of disease-related mortality or being connected to mechanical ventilation among patients hospitalized for COVID-19 (13).

Similar mortality rates between our vaccinated and unvaccinated patients may be attributed to the fact that the vaccinated group was relatively older and received inactivated vaccine. Ersan et al. (3) reported no significant difference in morbidity and mortality rates between the vaccinated (inactive vaccine) cases over 65 years with a definite diagnosis of COVID-19 compared to their unvaccinated counterparts. Multinational studies also highlighted that advanced age is a significant risk factor for mortality in COVID-19 disease (3, 14, 15). An Italy-based study reported COVID-19-related mortality rates to be 0.4% at the age of 40 and below, 1% between the ages of 50-60, 3.5% between the ages of 60-70, 12.8% between the ages of 70-80, and 20.2% at the age of 80 and above (14). In China, Wu et al. (15) reported mortality rates among COVID-19 patients as 0.4% among those aged 40 years and below, 3.6% among 60-70- year-olds, 8% among 70-80-year-olds, and 14.8% among those aged 80 years and older. In present study, vaccinated patients had significantly higher leukocyte, troponin,

and ferritin levels than the unvaccinated patients.In our study, vaccinated patients have older age and have more concomitant disease than unvaccinated patients These situation may explain higher level leukocyte, troponin, and ferritin levels

Risk factors other than age for a severe course and mortality in COVID-19 disease were previously reported to be male sex, obesity, smoking, and chronic underlying diseases (e.g., HT and DM) (3,16,17). In their study with vaccinated (inactivated vaccine) and unvaccinated patients aged 65 years and above, Ersan et al. (3) found no significant difference between the patients' ages (75.8±7.4 years and 73.8±8.0 years, respectively). In the same study, the overall mortality rate was 21.9% (33 patients), and it was reported that all patients who died were those who were followed up in the intensive care unit. While 19 (57.6%) of these patients were vaccinated, 14 (42.4%) were unvaccinated. The authors also found no significant difference between the mortality rates of the groups. Yet, there was a significant, positive correlation between the number of comorbidities and mortality. In our study, the rate of concomitant diseases was statistically higher in the vaccinated group (44; 69.8%) than in the unvaccinated group (34; 40.9%). Moreover, HT was significantly more prevalent in the vaccinated group than in the unvaccinated group (**Table**).

Ersan et al. (3) did not report significant differences in lymphopenia, CRP, ferritin, and D-dimer levels between vaccinated and unvaccinated patients. Considering the laboratory findings in this study, we found that the vaccinated group had significantly higher leukocyte, troponin, and ferritin levels than the unvaccinated patients.

In their placebo-controlled study with CoronaVac (inactivated vaccine), Tanrıöver et al. (17) reported the effectiveness of the vaccine as 83.5% after 14 or more days following the second dose among 10,029 participants (6,559 participants in the two-dose vaccine group and 3,470 people in the placebo group). In the same study, the frequency of vaccine-related adverse events was reported to be 18.9%. In both groups, while the most frequently reported systemic side effect was fatigue, the local side effect was pain at the injection site.

In another study comparing CoronaVac with BNT162b2 (mRNA vaccine), there was a negative correlation between age and neutralizing antibody formation. Accordingly, the neutralizing antibody titer was significantly lower in the group vaccinated with CoronaVac than those receiving BNT162b2 (3,18,19).

Some other studies revealed that mRNA and vector-based vaccines provide more efficient protection in the older adult population (11,20). Another study compared the severity of the COVID-19 disease between vaccinated (at least one dose of Pfizer-BioNTech or Oxford-AstraZeneca) and unvaccinated patients hospitalized in an intensive care unit in Saudi Arabia. The findings demonstrated that at least one dose significantly reduces the severity of the disease and is significantly associated with a reduction in 30-day all-cause mortality (21).

In a case-control study in the United States, Olson et al. (22) found the efficacy of the BNT162b2 vaccine to be 94% in preventing hospitalization for COVID-19, 95% among test-negative controls, 98% against admission to the intensive care unit, and 98% directly against COVID-19. In the study, it was reported that seven patients who died due to COVID-19 were unvaccinated. Overall, it was concluded that two doses of the BNT162b2 vaccine are highly effective against COVID-19-related hospitalization, admission to the intensive care unit, and the receipt of life support in the intensive care unit among hospitalized adult patients.

In their study in India, Muthukrishnan et al. (23) explored the efficacy of recombinant adenovirus vector vaccines on mortality associated with COVID-19. The study included 266 partially vaccinated patients (2 weeks after single-dose vaccination) and 184 full-dose vaccinated patients (2 weeks after 2 doses of vaccination). The researchers concluded mortality of 12.5% (23/184) among those who were fully vaccinated and 31.45% (309/984) among those who were not vaccinated. Thus, the mortality rate in unvaccinated patients was found to be statistically higher. Logistic regression analysis yielded that full vaccination and younger age were associated with survival.

Ersan et al. (3) studied 151 COVID-19 patients (78 patients who received two doses of inactivated vaccine and became ill 15 days after vaccination and 73 patients who were not vaccinated, received a single dose, or became ill within 15 days after two doses of vaccine) but could not detect significant differences between the vaccinated and unvaccinated groups by intensive care admission and intensive care mortality rate.

Similar mortality rates between our vaccinated and unvaccinated patients may be attributed to the fact that the vaccinated group was relatively older, had more comorbid diseases, and had their second dose after an average of 100.6 days following their first dose of inactivated vaccine.

Limitations

The present study is not free of a few limitations. This was a retrospective and single-center study, and we only considered hospitalized cases. Moreover, the number of patients who died in the groups was too low. Finally, all vaccinated patients received no vaccine other than an inactivated vaccine.

CONCLUSION

In conclusion, further clinical research involving more cases that received different COVID-19 vaccines is needed to uncover the factors affecting mortality and morbidity among vaccinated patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Training and Research Hospital Clinical Researches Ethics Committee (Date: 10.20.2021, Decision No: E-765/2021).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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